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Hemophagocytic Lymphohistiocytosis

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Malignancy Induced Hemophagocytic Lymphohistiocytosis

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Introduction

Hemophagocytic Lymphohistiocytosis is a rare, aggressive and life threatening condition characterized by excessive immune activation. In view of a variable clinical presentation, lack of specificity of the clinical and laboratory findings and outcomes limited by delay in identification warrants discussion to help in this challenging diagnosis.

HLH comes in two forms, primary and secondary HLH. Here we discuss secondary HLH which by prevalence can be due to viral infections (29%), other infections (20%), malignancies (27%), rheumatologic disorder (7%) and immune deficiency syndromes (6%). Among the cases related to malignancy, most are due to hematologic malignancy. In children hematologic malignancy related HLH is associated with B-lymphoblastic leukemia, and in adults likely T cell lymphomas.

Case Description

A 57-year-old female initially presented for a CT of the chest after failed outpatient treatment for pneumonia; initial imaging denoted diffuse lymphadenopathy, she followed up with Hematology/Oncology, having two fine needle aspirations with inconclusive results.

Approximately 2 months later she presented to our ED with progressive shortness of breath, hypoxia and chest pain associated with significant fatigue and cough. Her initial physical examination was significant for only bilateral crackles at the lung bases. CT PE was performed which showed significant supraclavicular lymphadenopathy and subsegmental PE along with bibasilar infiltrates. At this point lactic acid was performed which was elevated, and she was diagnosed with PE, pneumonia and sepsis and admitted to the MICU and started on broad-spectrum antibiotics and heparin drip.

While in the ICU General surgery was consulted for excisional biopsy of any reachable lymph node. Results from this biopsy showed Angioimmunoblastic T cell lymphoma with EBV driven polymorphous B cell lymphoproliferation. In post-op after the biopsy she became tachycardiac, tachypneiac and hypoxic. Over the next 5 days, she became significantly anemic, thrombocytopenic, febrile, hypercalcemic, hyperuricemic and hypofirbinogenemic, and developed significant splenomegaly of 17 cm with worsening lactic acidosis.

At this point HLH was considered and triglyceride levels along with ferritin and IL-3 (CD25) receptor were ordered. She was found to have significantly elevated ferritin and IL-2 along with high triglycerides and low fibrinogen. During this time she was also exhibiting tumor lysis syndrome with elevated LDH and uric acid, and became hemodynamically unstable; subsequently leading to the patients' death.

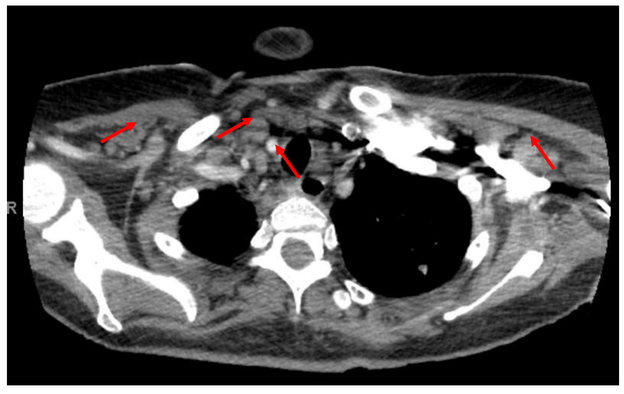
Labs

- AST:88
- ALT: 20
- INR:
- Creatinine: 1.38
- WBC: 10.8
- Hgb: 7.5
- Plts: 33
- Triglyceride: 541
- Ferritin: 9690
- Fibrinogen: 86
- Soluble IL-2 Receptor: 168,100

Photos

A diagnosis of HLH can be established if the patient either has a molecular diagnosis consistent with HLH or fulfills at least five of the following diagnostic criteria:

- Fever
- Splenomegaly
- Cytopenias (in ≥2 of 3 lineages in the peripheral blood)
  Hemoglobin <90 g/l (<100 g/l in infants <4 weeks old)
  Platelets $<100\times10^9$/l
  Neutrophils $<1\times10^9$/l
- Hypertriglyceridemia (≥2.99 mmol/l) and/or hypofibrinogenemia (≤4.41 µmol/l)
- Hemophagocytosis in the bone marrow, spleen, or lymph nodes without evidence of malignancy
- Low or absent natural killer cell cytotoxicity
- Hyperferritinemia (≥500 pmol/l)
- Elevated sCD25 levels ($\geq2.4\times10^6$U/l)



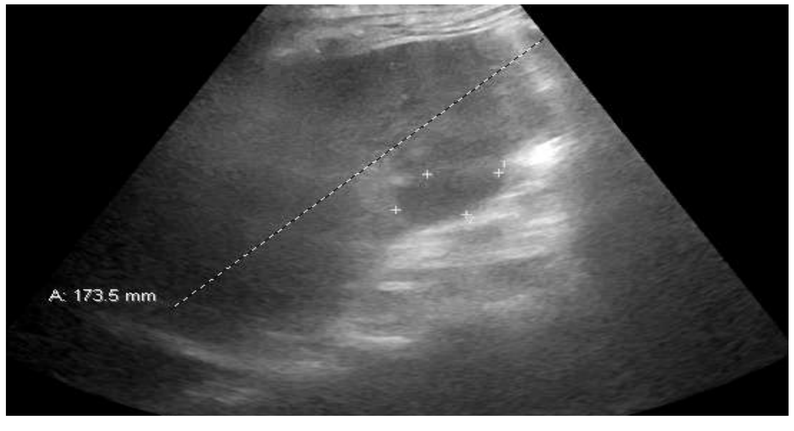


Figure 1. This figure illustrates the specific criteria required for diagnosis of HLH Figure 2. CT of the chest indicating lymphadenopathy Figure 3. Ultrasound indicating Splenomegaly

Discussion

HLH is a life-threatening condition due to ineffective immunity and uncontrolled hyper-inflammatory response. This is often a disease of the pediatric population, with the highest incidence in those <3 months. However more and more it is being found in adults even as old as 70 years of age. It can often be triggered by infection, malignancy, and autoimmune disease. There are familial forms of this disease as well which result from defects in NK cells and cytotoxic T-cells. Hemophagocytosis refers to the literal phagocytotic engulfment of hematopoietic cells by macrophages activated in the bone marrow. Macrophages in HLH also secrete excessive amounts of cytokines leading to tissue damage and organ failure. Normally NK cells and cytotoxic T cells work to eliminate, damaged, stressed, or unregulated cells. In HLH however these cells fail to do so and the normal feedback regulation is lost resulting in continued macrophage activation and cytokine production. Triggers that have been identified are often viral in nature, and often related to EBV.

HLH normally presents as a febrile illness, with multiple organ systems involved. They can present with a confounding picture as fever of unknown origin, hepatitis, or even encephalitis or meningitis. Along with fever patients will often develop splenomegaly, bicytopenias, will have elevated LFTs and triglycerides. One important marker is ferritin, which is often over 500 in 94% of patients. The main cytopenia's involved are anemia and thrombocytopenia with average hemoglobin around 7-8 and platelet counts around 70,000. Ferritin levels can often be increased in iron overload syndromes, sepsis, infections and liver failure, however at levels around 10,000 the specificity for HLH is 96%. Neurologic abnormalities are common in HLH, and can be variable from seizures, mental status changes, to ataxia. PRES syndrome can also be related to HLH. Pulmonary function and respiratory distress often occur with HLH, in and ARDS like fashion, which often requires mechanical ventilation.

The initial tests in HLH should be centered on that pathophysiology of the disease, including CBC w/ diff. coagulation studies, liver enzymes, Serum ferritin, LDH, and serum triglycerides. When clinical judgment leads you to a cause of HLH, further testing such as blood cultures, bone marrow evaluation, and imaging should be considered. Specialized testing can include Soluble IL-2 receptor, NK cell function, and flow cytometry. Five of the eight criteria for HLH are required for a diagnosis.

Treatment for patients that are critically ill with HLH is centered on HLH specific chemotherapy, which includes Etoposide and high dose steroids (dexamethasone), and intrathecal treatments if CNS involvement is found. Supportive treatment with transfusions for anemia and thrombocytopenia should be given as well to maintain platelet counts over 50,000. Long-term cure or the disease requires hematopoietic cell transplant, and in the case of malignancy related HLH would require allogenic transplant to stop recurrent HLH. The median survival of patient with HLH is 54% at 6 years. Higher ferritin levels at diagnosis, and slow decline in ferritin during treatment is also a poor prognostic factor.

Conclusion

HLH is a clinically rare condition that is increasing in prevalence and is still significantly under recognized today. This case illustrates the necessity for early identification of HLH in the setting of predisposing conditions such as malignancy and initiation of treatment, especially in the setting of an unclear clinical picture delaying diagnosis. The high morbidity and mortality associated with this condition can be attributed to under recognition and the fulminant course of the disease, with the need for therapy to be initiated early for any reasonable attempt to provide a favorable outcome. While strides have been made recently in regards to treatment options increasing survival, this diagnosis remains devastating and much work remains to raise awareness and improve effectiveness of treatments.

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